

REMARKS

Applicants respectfully request reconsideration and further examination of all pending claims presented herein.

I. Status of the Claims and Amendment C

In this Amendment C, claims 44-67, 71-150 and 155-163 have been canceled for being directed to subject matter of non-elected inventions, consistent with the previously issued Restriction Requirement and Applicants' response thereto. Applicants respectfully reserve the right to pursue the subject matter of these claims in one or more divisional applications at a later date.

Accordingly, claims 1-22, 24-43, 68-70 and 151-154 are now pending in the present application. In this Amendment C, claims 1, 34-38, 68, and 152-154 have been amended to more particularly claim certain embodiments. Support for the amendments to claims 1 and 34-37 may be found throughout the specification and, more specifically, in paragraphs [0009] and [0012] of Applicant's published application (Patent Application Publication No. US 2005/0182257), as well as original claim 38 therein. Claim 38 has been amended simply to remove a redundancy created by the amendment to claim 1, from which it depends. Finally, support for the amendments to claims 68 and 152-154 may be found throughout the specification and, more specifically, in paragraphs [0009] and [0012] of the noted published application.

II. Priority

The Office has acknowledged Applicant's claim to priority under 35 U.S.C. 119(e), but has noted that the present Application had not been amended to recite the priority information in the first sentence. This priority statement has been added by way of amendment in this Amendment C.

In this regard it is to be noted that the priority information being added by amendment herein was previously submitted in the executed Declaration, which was filed with the 371 U.S. National Application of PCT Application Serial No. PCT/US03/04498 on July 14, 2004. Additionally, U.S. Provisional Patent Application Serial No. 60/360,321, which was referenced in the Executed Declaration, was clearly noted as a priority document upon which this PCT application was based and from which it claimed priority. However, in spite of these clear references to the noted U.S. Provisional Patent Application, the priority information related thereto was not reflected in the filing receipt mailed April 21, 2005, apparent due to an oversight by the Patent Office when the filing receipt was issued.

In view of the foregoing, Applicant respectfully submit that a petition under 37 C.F.R. 1.78(a) and the surcharge fee under 37 C.F.R. 1.17(t) are not needed here.

III. Claim Rejections under 35 U.S.C. § 103

Pending claims 1-22, 24-43, 68-70 and 151-154 are rejected under 35 U.S.C. 103(a) as obvious in view of, separately, Perterson (*Journal of Chromatography*, 188 (1990) 420-425, hereinafter referred to as "Peterson"), Vandenberghe (*Therapeutic Drug Monitoring*, 4:307-314, hereinafter referred to as "Vandenberghe"), and Matantseva (Khimiya prirodnikh Soedinenii, English translation, hereinafter referred to as "Matantseva"). In response thereto, Applicant respectfully submits that for the reasons set forth below independent claims 1, 34-37, 68 and 152-154, as well as all claims depending therefrom, are not obvious in view of the cited references.

As set forth in M.P.E.P. §2143, in order for the Office to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art references must disclose each and every element of the claim; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references; and (3) there must be some reasonable expectation of success. Further, an obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of the case. The common sense of those skilled in the art can demonstrate why some modifications and/or combinations would have been obvious where others would not. Finally, as noted in the Examination Guidelines For Determining Obviousness Under 35 U.S.C. §103(a) in view of the Supreme Court decision in *KSR Int'l Co. v. Teleflex, Inc. et al.*, the Office must provide a reasonable explanation to support any obviousness rejection.

Applicant respectfully submits the Office has failed to establish a *prima facie* case of obviousness for a number of reasons. First, **each and every element of the claims has not been disclosed or suggested** by the individually cited references. Additionally, or alternatively, there is simply **no motivation** to modify the individually cited references as suggested by the Office, in order to arrive at the claimed subject matter.

Initially, it is to be noted that Applicant's claimed methods are directed to a method for separating morphine from a crude narcotic alkaloid solution using **preparative chromatography** and a **preparative chromatography column**, as recited in independent claims 1, 34-37, 68 and 152-154. In contrast, each of the references individually cited in the present Office Action are directed specifically and solely to **analytical chromatography**, and furthermore **do not even reference** to the use of a preparative chromatography. Accordingly, the individually cited references clearly **fail to disclose or suggest each and every element** of the claimed methods. In addition, the individually cited references provide **no motivation** to one of

ordinary skill in the art to modify the methods disclosed therein, in order to arrive at the claimed methods, in view of the **total silence** of each reference with respect to preparative chromatography.

With respect to the motivation to modify the individually cited references, it is to be further noted that, as explained in Applicant's specification, use of analytical chromatography to separate narcotic alkaloids does not lead one of ordinary skill in the art to the use of preparative chromatography; rather, this would arguably **teach** one of ordinary skill in the art **away** from using preparative chromatography. (See Applicant's specification, paragraphs [0009] and [0010] the noted published application.) Applicant explains therein that unlike preparative chromatography, wherein the objective is to recover the desired feed with the required purity, analytical chromatography requires complete separation of each peak, as measured typically by ultraviolet absorbance. Complete separation of peaks is achieved by loading an **infinitely small mass** of the feed onto the column, and using a **small particle size diameter** (often less than 5 micrometers, or 196.85 microinches) in the stationary phase. The small particle size generates **high pressures**, which mandate the use of very large, strong and expensive chromatography equipment, thus negating the commercial viability for this analytical process. Furthermore, for commercial viability, the equipment would be very large, given that an infinitely small mass of feed is loaded in each run. (See Applicant's specification, paragraph [0009] of the noted published application).

In contrast, the objective of preparative chromatography is to recover the desired feed component with the required purity. The desired component can be **recovered with impurities**, so long as the impurities are within specification limits. The particle size of the stationary phase is small enough to achieve the separation, but is often greater than 10 micrometers (393.70 microinches), which at a minimum is generally **twice as large** as the largest particle size of the stationary phase typically used in analytical chromatography. This limits the pressure drop generated. Also in contrast to analytical chromatography, in preparative chromatography the **maximum** amount of feed is loaded on the column, with primary constraint being that of attaining the desired product quality. This allows the product to leave the column with a maximum concentration, which then minimizes the size of the downstream equipment, especially any evaporating or concentrating units. (See Applicant's specification, paragraph [0009] of the noted published application). Moreover, the differences between analytical chromatography and preparative chromatography involve more than simply scaling up a single process. The problems encountered in each, and the solutions to those problems are quite different.

To illustrate, the following differences between Applicant's claimed preparative chromatographic method and the analytical chromatographic methods of the cited references are to be noted:

- (1) Peterson achieves complete peak separation, and is able to quantitate morphine to 1 ng, using analytical chromatography with an elution rate of 2.0 mL/min, resulting in a back pressure of 13.8 MPa (2000 p.s.i.), a column with dimensions of 30 cm X 4 mm, and a sample size of 1 μ L. (Peterson, page 421, paragraphs 1, 4 and 5). Nothing in Peterson, from the pressure used, the column dimensions or the sample size, would lead one of ordinary skill in the art to use the same method for preparative chromatography.
- (2) Similarly, Vandenberghe is concerned with analytically determining a very low concentration of morphine in a very small sample, *i.e.*, a serum or plasma sample from a child from 0 to 5 years old. (Vandenberghe, page 307). Vandenberghe was able to determine to 1 μ g/L from a 100 μ L specimen size using an elution rate of 1 mL/min, 1000-1700 psi, a 4 mm X 30 cm column, and a sample injection size of 50 to 90 μ L. (Vandenberghe, pages 309-310). As with Peterson, because of the minute sample size, small diameter column, and high pressures used, nothing in Vandenberghe leads one of ordinary skill in the art to use chromatography as a preparative method.
- (3) Finally, like Vandenberghe and Peterson, nothing in Matantseva would lead one of ordinary skill in the art to choose chromatography as a preparative method. Matantseva discloses the use of analytical chromatography in the analysis of pharmaceutical preparations, such as opium alkaloids. While Applicant cannot tell the precise conditions from the translation of Matantseva, it is clear that Matantseva is directed to quantitative separation, rather than a preparative method, as claimed by Applicant. (See, *e.g.* Matantseva, first two paragraphs).
- (4) In contrast, Applicant uses a preparative chromatography column, which in one exemplary system is at least 5 cm in diameter, which is more than **10 times** greater than the columns used in Peterson or Vandenberghe. Similarly, the amount of crude narcotic alkaloid solution used is much greater than the 1-90 μ L of the references. Applicant claims at least 0.255 grams (0.009 ounces), preferably at least 6.38 grams (0.225 ounces), and more preferably at least 8.50 grams (0.300 ounces) of narcotic alkaloid solution. Applicant's sample volumes are at least **3 times** to more preferably **100 times** greater than the largest volume in Vandenberghe. Applicant's sample size is at least **300 times** greater, and more preferably at least **10,000 times** greater, than the sample size in Peterson. Furthermore, as pointed out by Applicant in the specification, there are also differences in stationary phase particles size, as well as pressures used.

Thus, while the Office appears to contend that the difference between analytical chromatography and preparative chromatography is merely within the routine skill of an artisan in this field, Applicant respectfully points to the reasons outlined in the specification and illustrated in the cited references as to why this is simply not the case.

In view of the foregoing, Applicant respectfully submits that **none** of the cited references **disclose or suggest each and every element** of Applicant's claimed invention. Furthermore, Applicant submits that there is simply **no motivation** for one of ordinary skill in the art to modify the cited references in order to arrive at the claim subject matter. Applicant therefore submits that a *prima facie* case of obviousness has not been made, and that all pending claims are patentable over the cited references. Accordingly, Applicant requests withdrawal of the rejection of all pending claims.

IV. Objection to Claims as Containing Non-elected Subject Matter

Claims 1-22, 24-43, 68-70 and 151-154 are objected to for containing non-elected subject matter. In response thereto, the non-elected subject matter has been removed from claims 1, 34-38, 68 and 152-154, and thus all claims depending therefrom, by way of amendment. Accordingly, Applicant respectfully requests withdrawal of this objection.

CONCLUSION

In view of the foregoing, Applicants respectfully request favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account 13-1160 for any fees due for the submission of this Amendment C.

Respectfully submitted,



Craig D. Siman, Reg. No. 60,137
Mallinckrodt Inc.
675 McDonnell Boulevard
Hazelwood, Missouri 63042
(314) 654-3960

Via EFS
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